Jazz Pharmaceuticals www.JazzPharmaceuticals.com

Submitted by
Francois Di Trapani, Vice President Global Scientific Affairs
Jazz Pharmaceuticals
3170 Porter Drive
Palo Alto, CA 94304
Phone: 650.496.2759
Email: francois.ditrapani@jazzpharma.com

Date of request: November 15, 2017

NCCN Acute Myeloid Leukemia Panel

Re: Request for review of clinical data and recommendation for defibrotide in the NCCN Clinical Practice Guidelines in Oncology® - Acute Myeloid Leukemia (AML)

On behalf of Jazz Pharmaceuticals, I respectfully request the NCCN Acute Lymphoblastic Leukemia Panel to review the enclosed FDA approved label[1] and clinical studies[2-6] in support of the inclusion of DEFITELIO® (defibrotide sodium [defibrotide]) as the treatment of hepatic veno-occlusive disease (VOD) in AML.

FDA Clearance: DEFITELIO (defibrotide sodium) is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).[1]

Suggested Changes: We respectfully ask the NCCN Panel to consider adding the following:

AML-C 1 of 2 "Supportive Care": New bullet

- Hepatic VOD is a rare but life-threatening complication following hematopoietic stem cell transplant (HSCT) or chemotherapy without HSCT:
  - Defibrotide for treatment of patients who develop hepatic VOD.
  - Treatment with defibrotide has been shown to result in a 38% to 49% survival rate at 100 days after HSCT in patients with VOD with multi-organ dysfunction (MOD), compared with a historical control rate of 21% to 31%. In 488 patients with VOD without MOD post HSCT, from a large expanded access protocol, defibrotide therapy resulted in 69% survival at 100 days.
  - In patients who developed VOD post-chemotherapy without HSCT, defibrotide therapy resulted in 66% survival with MOD and 81% survival without MOD at 70 days post initiation of defibrotide.

Rationale Summary:
Defibrotide is the first and only FDA-approved therapy for treatment of hepatic VOD with renal or pulmonary dysfunction following HSCT,[1] a rare and life-threatening liver complication that can occur following HSCT or chemotherapy. Although rare, hepatic VOD with multiorgan dysfunction is associated with a very high mortality rate of up to 80%.[7] Use of defibrotide resulted in 38% to 49% survival at 100 days after HSCT in patients with MOD, in a wide variety of underlying malignancies, compared with a historical control rate of 21 to 31%.[1-5] In 488 patients with VOD without MOD post HSCT from a large expanded access protocol, defibrotide therapy resulted in 69% survival at 100 days.[5] Based on a posthoc analysis from a large expanded access protocol, in patients who developed VOD after a variety of chemotherapy regimens without HSCT (13% are AML patients), use of defibrotide resulted in 74% survival at 70 days.[6] Inclusion of defibrotide as a therapy can provide an effective option to patients affected by this frequently fatal condition.

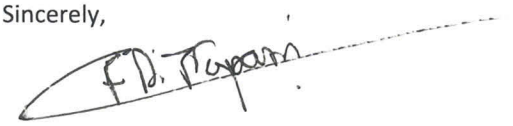
Published Literature Support:
Defibrotide is not approved by the FDA for use in patients with hepatic with VOD without MOD following HSCT nor in patients who developed VOD post-chemotherapy without HSCT.

Post-HSCT
Defibrotide was studied in 2 prospective trials and an expanded access study in patients diagnosed with hepatic VOD after HSCT.[2-5] In the phase 3 study,[2] defibrotide was administered intravenously at 25 mg/kg daily in 4 divided doses, infused over 2 hours every 6 hours for a minimum of 21 days. The study involved a total of 134 patients; 28.4% of the defibrotide-treated patients and 25% of patients in the control group had AML as the underlying disease. Defibrotide treatment resulted in 38.2% survival at day +100 post HSCT in 102 patients with established hepatic VOD and MOD, compared with 25.0% in 32 historical controls identified out of 6867 medical charts of HSCT patients by blinded independent reviewers (estimated difference adjusted for propensity score=23%, 95.1% CI, 5.2-40.8; *P*=0.0109, propensity-adjusted analysis). Observed day +100 complete response rates equaled 25.5% for defibrotide and 12.5% for controls (estimated difference adjusted for propensity score=19%, 95.1% CI, 3.5-34.6; *P*=0.0160). Hypotension was the most common AE in both groups (39.2% with defibrotide, 50% for historical controls). Overall, there was no difference in the incidence of common hemorrhagic AEs (64% with defibrotide and 75% with historical control).

Under a broad expanded-access treatment protocol involving 1000 patients with VOD and with or without MOD post HSCT,[3,5] day +100 survival was 58.9% (95% CI, 55.7%-61.9%) in patients treated with defibrotide. Overall, the study included 261 (26.1%) patients with AML. Among 512 patients with MOD, 49.5% (95% CI, 45.0%-53.0%) were alive at day +100 post HSCT. In patients without MOD, the +100 day post-HSCT survival was 68.9% (95% CI, 64.5%-72.9%). These results were consistent in an earlier phase 2 study that enrolled 149 patients with VOD and MOD; overall complete response rate was 46% and day +100 post-HSCT survival rate was 42%.[4] The expanded-access treatment protocol data reported grade ≥3 treatment-related AEs in 3% of patients with no treatment-related deaths. The incidence of grade ≥3 expected AEs was 55% with the most common being renal failure (31%), hypotension (29%), hypoxia (26%), and pulmonary AEs (22%). Defibrotide-related toxicity resulting in treatment discontinuation occurred in only 4% of patients.

Post-chemotherapy without HSCT
In a posthoc analysis, the efficacy of defibrotide post-chemotherapy without HSCT has also been studied under the expanded access protocol. A total of 82 patients (13% with AML) received defibrotide within 30 days of starting a variety of chemotherapy regimens without HSCT.[6] The 70-day Kaplan-Meier estimate survival was 74.1% (65.8% and 81.3% in patients with and without MOD, respectively).[6] Further exploratory analysis in this subset of patients suggests that earlier defibrotide initiation post-VOD diagnosis was associated with improved day +100 survival.[8]

Sincerely,



Francois Di Trapani
Vice President Global Scientific Affairs

References (**enclosed**):
1. DEFITELIO prescribing information. 2016. Jazz Pharmaceuticals, Inc.
2. Richardson PG, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656-65.
3. Richardson PG, et al. Defibrotide for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome: interim results from a treatment IND study. Biol Blood Marrow Transplant. 2017;23(6):997-1004.

4. Richardson PG, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 2010;16(7):1005-1017.
5. Richardson PG, et al. Efficacy and safety of defibrotide in the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome following hematopoietic stem cell transplantation: Final subgroup analysis. 2017. EHA Annual Congress. Abstract P748.
6. Kernan NA, et al. Efficacy and safety of defibrotide to treat hepatic veno-occlusive disease/sinusoidal obstruction syndrome after primary chemotherapy: A post hoc analysis of final data. 2017. ASCO Annual Meeting. Abstract S504.
7. Coppell J, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157-168.
8. Kernan N, et al. Timing of defibrotide initiation post-diagnosis of hepatic veno-occlusive disease/sinusoidal obstruction syndrome after primary chemotherapy: exploratory analysis of an expanded-access protocol. 2017. Presentation at the EHA Annual Meeting. Abstract P650.